The dynamics of selected local inflammatory markers to talc in the treatment of malignant pleural effusions

Petr Habal[a], Karolina Jankovicova[b], Nedal Omran[a], Katerina Kondelkova[b], Jan Krejsek[b], Jiri Mandak[a]

Background. Malignant pleural effusions accumulate in the space between the visceral (inner) layer covering the lungs and the parietal (outer) layer covering the chest wall. Larger effusions compress the pulmonary parenchyma resulting in increasing dyspnoea. Treatment is always local and palliative. Among others, chemical pleurodesis using talc can be performed in selected patients. Talc is hydrated magnesium silicate (chemically $H_2Mg_3(SiO_3)_4$) and has been used for pleurodesis since 1935. Videothoracoscopic talc powder insufflation (talc poudrage) is the most effective. However, markers of inflammatory reactions to extraneous substances like talc are not fully understood. The aim of this study was to assess the course of local inflammatory changes in the pleural cavity after talc insufflation.

Methods. The Department of Cardiac Surgery of the Faculty of Medicine and University Hospital in Hradec Kralove, treated 47 patients aged 65 on average; 29 males and 18 females with proven recurrent malignant pleural effusion of various aetiologies from January 2009 to December 2010. They were retrospectively divided into group A (40 patients) without recurring effusion, and group B (7 patients) with recurring effusion and the need for thoracentesis or chest drainage during the 9-month monitoring.

Results. Major findings were made in soluble forms of cell receptors. Group B showed statistically higher levels of the anti-inflammatory form of sCD-163 receptor in pleural fluid before the talc poudrage. This showed limited ability to create an adequate inflammatory response to external stimuli. This group also showed lower levels of the inflammatory form of sTLR-2 receptor immediately after the talc insufflation. This revealed low local reactivity to external stimuli. The effect of the treatment was not influenced by morphologic tumour type. No statistically significant differences in postoperative complications were found. This confirmed the safety of both videothoracoscopy and treatment.

Conclusions. There was no correlation between the type of malignant affection and the outcome of the chemical pleurodesis. Patients with relapsing effusion have higher values of concentration of anti-inflammatory sCD-163 in pleural fluid even before the application of talc, and lower levels of concentration of inflammatory sTLR-2 immediately after application of talc.

Key words: malignant pleural effusion, thoracoscopy, talc, sCD-163, sTLR-2

[a]Department of Cardiac Surgery, Faculty of Medicine in Hradec Kralove, Charles University in Prague and University Hospital in Hradec Kralove, Czech Republic
[b]Department of Clinical Immunology and Allergy, Faculty of Medicine in Hradec Kralove, Charles University in Prague and University Hospital in Hradec Kralove
Corresponding author: Jiri Mandak, e-mail: jiri.mandak@centrum.cz

INTRODUCTION

Malignant effusion takes place in the pathologically changed space between the parietal and visceral pleura most often in patients with cancer. Under physiological condition, the pleural cavity is the space between parietal and visceral pleura (10-20 μm width), which is filled with serous fluid- 0.1 - 0.2 mL/kg total body weight. The pleural surface is enlarged by the microvillus system. In the adult, the surface of the pleural membranes covers about 4 square meters[1].

Pleural effusion is caused by either exceeding the resorptive capacity of the pleura, which is about 700 mL/day (e.g. in the case of increased hydrostatic pressure, decreased oncotic pressure, decreased intrapleural pressure, increased capillary permeability or fluid movement from the peritoneal cavity etc.) or decrease in the absorption capacity of the pleural lymphatic drainage system (in case of malignant involvement of the lymphatic vessels), or a combination of both causes[2,3].

Malignant effusions account for about 15-30% of all pleural effusions, most often in cases of breast and lung carcinoma[4,5]. In palliative oncological treatment (POT), relieving thoracentesis and chest drainage are performed[6].

Repeating these can cause pneumothorax or haemothorax and damage to pulmonary tissue or intercostal vessels. Empyema of the thorax is very serious.

Talc insufflation thoracoscopically can be done in selected groups of patients with malignant pleural effusion and preserved lung expandibility[7],.Effective contact of parietal and visceral pleura due to the talc then ensures no fluid return[8]. In case of sustained collapse of the pulmonary parenchyma after thoracentesis (trapped lung syndrome) pleurodesis is contraindicated and other methods of treatment should be considered[9]. The principle of pleurodesis is elimination of the space between

the visceral and parietal pleura by inducing aseptic pleuritis[10,11]. This procedure is called chemical pleurodesis. Many substances have been tested to achieve this aim e.g. silver nitrate, iodopovidone, doxycycline, bleomycine and *Corynebacterium parvum* vaccine with different outcomes[12]. The use of *Corynebacterium parvum* for pleurodesis is not recommended due to the increasing number of anaphylactic reactions[13,14].

The most effective is application of talc in powder[15]. This is effective in up to 90% of cases[16]. The use of talc is based on experience, with a dose up to 5 g (ref.[10,17]).

To date, there has only been sporadic evaluation of the general inflammatory reactions of the organism to extraneous substances while evaluation of local inflammatory markers for use in clinical medicine is the subject of ongoing clinical studies[18,19]. In the past, some biochemical markers of effusion in relation to survival prognosis were examined. For example, if the concentration of glucoses is < 600 mg/L, the prognosis is adverse[20].

More recent studies have evaluated the relation of survival time and pleurodesis success rate to pH of pleural fluid[21]. Treatment success can be evaluated by a large number of markers such as adenosindeaminase[22].

MATERIAL AND METHOD

From January 2009 to December 2010, at the Department of Cardiac Surgery of Medicine Faculty of Charles University and University Hospital in Hradec Kralove, 47 patients with cytologically proven recurring malignant pleural effusion were recommended for thoracoscopic talc poudrage.

The functional status of the patient was assessed using the Karnofsky Performance Status (KPS) index > 75%, and a realistic prognosis of survival time (LE) > 3 months in relation to basic diagnosis. The patients consisted of those with proven re-expansion of pulmonary tissue by fluoroscopy after removal of the effusion by previous thoracentesis.

The removal of the effusion was performed by videothoracoscopy, gradually in portions of 500 mL to prevent complications – re-expansion pulmonary oedema (RPE). After removing the fluid, a biopsy of parietal pleura was performed and 5 g of talc in powder form was applied. After talc poudrage a visual check for bleeding and re-expansion of the lung was performed. A chest tube was inserted using a video camera port.

Pleural fluid examination was done at three intervals during pleurodesis: 1st - before the thoracoscopic procedure, 2nd - 2 h after the terminating thoracoscopic procedure with talc insufflation 3rd - 24 h after the thoracoscopic procedure. The samples were examined for selected indicators of inflammation. The waste via chest drain over 24 h was < 150 mL. The effect of pleurodesis was evaluated by ultrasound at 1, 3, 6, 9 months.

Statistical analysis

Flow cytometry data were analysed by FlowJo software (Tree Star, USA). Clinical data, flow cytometry results and ELISA results were statistically analysed by MedCalc statistical software. Comparison between pleural effusion collection in the three intervals was assessed by paired t-tests or by Wilcoxon test according to the normality of the data. Differences between groups were tested by t-tests or Mann-Whitney test according to the normality of the data. Categorical data were tested by the Fisher exact test. Statistical significance was set at $P=0.05$.

The study protocol was approved by the Ethics Committee of the University Hospital in Hradec Kralove and informed consent was obtained from all participants.

RESULTS

Patients with pleural carcinomatos is of various aetiologies consisted of 29 (61.7%) men and 18 (38.3%) women (Table 1), aged from 42 to 80 years old, average 65 years old. The average time of operation was 44 ± 12 min. The average time of thoracoscopic drainage was 5 ± 2 days. The average time of hospitalization was 7 ± 2 days. The cause of one death 28 h after the operation was hypercapnic respiratory insufficiency.

Retrospectively, the patients were divided into Group A (40 patients) treated successfully without recurring effusion, and Group B (7 patients), where during the 9th - month of monitoring, it was necessary to perform repeated thoracentesis or chest drainage due to recurring effusion (Table 2).

Table 1. Basic diagnoses depending on the sex of patients.

Diagnosis	Male (%)	Female (%)
Carcinoma of lungs		
Metastases	15 (51.7)	2 (11.1)
- breast	0	6 (33.3)
- ovary	0	2 (11.1)
- GIT	8 (27.5)	2 (11.1)
- lymphoma	1 (3.4)	0
- Grawitz	0	1 (5.5)
Malignant mesothelioma	3 (10.3)	2 (11.1)
Malignant thymoma	2 (6.8)	0
Neurofibrosarcoma	0	1 (5.5)
Malignant struma	0	1 (5.5)
Chondrosarcoma	0	1 (5.5)
Σ	29	18

The groups differed in volume of effusion in the time of admission to the operation. At the time of discharge, there were no statistically significant differences in effusion volume. During the first check up after 1 month, Group B showed a significant rise in effusion volume and the trend to statistical difference lasted for the whole monitored period.

The dynamics of local inflammatory manifestations were monitored by changes in pleural values of anti-inflammatory soluble sCD-163 receptor. The concen-

Table 2. Development of pleural effusion quantity between Groups A and B in mL.

Time (month)	A	B	*P* - value
Ad	1000 (500 - 2000)	1500(1000 - 2500)	0.0014
D	200 (100 - 500)	400 (300 - 600)	0.121
1	200 (100 - 500)	800 (300 - 1000)	<0.001
3	250 (150 - 500)	700 (300 - 1000)	<0.001
6	250 (150 - 400)	950 (800 - 1250)	<0.001
9	250 (200 - 400)	1150 (850 - 1200)	<0.001

* - median (minimum – maximum), Ad - admission, D - discharge
A - group without exudate relapsing, B - group with exudate relapsing

Table 3. Development of local inflammatory reaction in Groups A and B - sCD-163 (ng/mL) in pleural fluid.

Time (h)	A	B	*P* - value
0	1128 (425 - 5541)	4275 (2353 - 4525)	0.001
2	936 (45 - 2231)	2346 (1118 - 5524)	0.028
24	695 (314 -1645)	1030 (658 - 1479)	0.10

* - median (minimum – maximum),A - group without exudate relapsing, B - group with exudate relapsing

Table 4. Development of local inflammatory reaction in Groups A and B - sTLR-2 (ng/mL) in pleural fluid.

Time (h)	A	B	*P* - value
0	33.5 (0 - 718)	33 (12 - 236)	0.638
2	180 (27 - 656)	50 (0 - 204)	0.002
24	415.5 (17 - 987)	224 (116 - 431)	0.016

* - median (minimum – maximum), A - group without exudate relapsing, B - group with exudate relapsing

trations of this receptor showed statistically significant differences between Groups even before the talc insufflation (P<0.001). A statistically significant difference between Groups A and B was still noticeable 2 h after the talc instillation into pleural cavity (P=0.028) (Table 3).

The dynamics of changes in concentrations of inflammatory soluble sTLR-2 receptor values in pleural effusion showed a significant rise in patients with successful treatment effects (A) as early as 2 h after the talc poudrage (*P*=0.002) and this rise was recorded during the whole monitored period. Input values in both groups were identical (Table 4).

DISCUSSION

There was no difference between the groups in basic demographics. There was no correlation between type of malignancy and treatment outcome. This has two aspects. First, it is a correct indication for surgical interventions in the remission of the basic disease. Second, any pleural tumorous disease due to effusion is similar. In malignancies, the mechanism of effusion development is not only due to blockage of lymphatic capillaries but also increase in capillary permeability and imbalance of the Starling equation which regulates reabsorption of pleural fluid.

A negative outcome of pleurodesis can be determined by the size of the tumour mass in the pleural cavity. Another factor is atelectatic involvement of the lung parenchyma caused by endobronchial tumour obstruction, which can cause trapped lung syndrome. This can explain the low success rate of the pleurodesis in cases of mesothelioma and lung cancer[23,24].

Talc has a direct effect on tumour mass in the pleural cavity. It may suppress angiogenesis via endostatin and affect the apoptosis of tumour cells. In experiments, cultured rabbit pleural mesothelial cells (PMC) were exposed to talc for 6, 24, or 48 h and assessed for viability, necrosis, and apoptosis by flow cytometry[25].

Pleurodesis by talc is the optimal treatment for malignant pleural effusion. Talc particles directly induce mesothelial cells to produce inflammatory cytokines, mainly IL-8, VEGF (vascular endothelial growth factor), and MCP-1 (monocyte chemotactic protein-1) (ref.[26]). These pro-inflammatory changes are followed by rapid polymorphonuclear neutrophil influx into the pleural space[27]. We observed this trend in our study as relative number of polymorphonuclear neutrophils increased from 33.07% preoperatively to 90.21% after talkage. There is also evidence that talc enhances intercellular adhesion molecule-1 (ICAM-1) expression in pleural mesothelial cells[28]. Pleural mesothelial cells treated by talc secrete bFGF

(basic fibroblast growth factor) and TGFβ (transforming growth factor β) responsible for fibroblast activation, and enhanced fibrogenesis including collagen production resulting in effective pleural fibrosis[29]. Surgical intervention involves severe operational trauma. Anaesthesia and surgery result in changes in the dynamics of inflammatory indicators[30]. This results in activating the coagulation and fibrinolytic blood system, and triggering the cascade of the inflammatory response[31,32]. The beneficial effect of the inflammatory reaction is in its participation in the defence against infective agents. The result of a successful reaction is the healing of damaged tissue[33].

The intensity of the inflammatory reaction depends among others on extraneous material. For this reason, the reaction in cardio surgical operations using extracorporeal circulation is stronger than that in operations that do not use it[34-36].

In the small number of operations of this study, we aimed to trigger an inflammatory reaction and increase its effect using an extraneous substance. We can measure a number of changes in the general reaction of the organism. General inflammatory changes are highly unspecified manifestations.

External stimuli induce danger signals in the body and identification of these is mediated by Toll-like receptors (TLR) (ref.[37]). The dynamics of general changes of the receptor response to inflammatory stimuli is known mostly from experiments[37,38].

The expression of TLR-2 molecule on polymorphonuclear granulocytes has been studied with respect to infection, sepsis, surgical stress and other medical interventions. This early TLR-2 down-regulation may be the result of externalizing entire molecules rather than transcriptional regulation of TLR-2 biosynthesis[39,40]. The intensity of TLR-2 expression on granulocytes is also significantly reduced during cardiopulmonary bypass surgery[41]. Our study showed down-regulation of TLR-2 expression on granulocytes during talc pleurodesis. However, we can only speculate about the direct effect of talc particles on granulocytes, cytokine influence or a combination of both.

CD-163 is a member of the scavenger receptor super family class B of the first subgroup. It is mapped to the region p13 on chromosome 12. This scavenger receptor is selectively expressed in cells of monocyte and macrophage lineage exclusively. It also has other functions. It participates in adhesion to endothelial cells, in tolerance induction and tissue regeneration. Other very important functions of CD-163 are the clearance of hemoglobin in its cell-free form and participation in anti-inflammation in its soluble form, exhibiting cytokine-like functions[42].

Our patients showed high levels of anti-inflammatory receptor sCD-163 even before the application of talc in Group B in which the treatment was not successful. We can assume that these patients were exposed to other external factors causing inflammatory reactions. However, there were no statistically significant differences between the groups in general inflammatory indicators before the operation. There was no significant difference between the groups between the operation and the last thoracentesis, which could have influenced local changes in inflammatory indicators.where we can judge that a different reactivity of monitored indicators was influenced by different state of "readiness" or "exhaustion" of the organism.

When talc is insufflated in the pleural cavity, the inflammatory reaction, which causes chemical pleurodesis, can also produce adverse reactions. The failure of internal regulative mechanisms can cause serious organic damage with fatal results. It is not yet possible to predict the intensity of inflammatory reaction to external stimuli in order to prevent these complications.

The first efforts to influence the inflammatory process were experimental. Results, extrapolated from experiments, often fail in clinical practice. The examination of local parameters of inflammatory reactions, which would enable us to make clinical decisions, is still in the experimental stage[43].

In clinical practice we work with a highly genetically heterogeneous spectrum of patients. For this reason, we can expect various inflammatory reactions.

CONCLUSIONS

In contrast to other studies, we found no correlation between the type of malignancy and the outcome of chemical pleurodesis.

No significant postoperative complications were recorded. This supports the safety of the videothoracoscopic method and chosen procedures.

In the current treatment procedures, inflammatory reaction on both parietal and visceral pleura only partially influences the resulting treating effect. The success of the reaction is influenced by biological status and metabolic activity. Effective, durable of both pleural membranes is essential.

For clinical practice, examination of sCD-163 in routine analysis using the ELISA method on samples of pleural fluid could be done. The fee for this examination is around 25 Euros.

To date, it has not been possible to influence systematically the pathological parameters corresponding to the sampled local inflammatory markers. The differences in results can be used to diagnose within hours after the operation, in some cases before hand and in selected patients it is hence possible to apply talc via the per-operatively placed chest drain.

From analysis of the dynamics of local immunological indicators we have gained some original knowledge. Patients with relapsing effusion have higher values of concentration of the anti-inflammatory sCD-163 in the pleural fluid even before the application of talc, and lower levels of concentration of inflammatory sTLR-2 immediately after application of talc.

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CONFLICT OF INTEREST STATEMENT

Author's conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

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